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Institute for Pharmaceutical Sciences, Faculty of Pharmacy, Utrecht University, P.O. Box 80082, NL-3508 TB Utrecht (NL).

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(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

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(71) Applicant (*for all designated States except US*): QUADRANT HEALTHCARE (UK) LIMITED [GB/GB]; 1 Mere Way, Ruddington, Nottingham NG11 6JS (GB).

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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): ADAN, Roger, Antonius, Henricus [NL/NL]; Dept. of Medical Pharmacology, Rudolf Magnus Institute for Neuroscience, Utrecht University, Faculty of Medicine, Universiteitsweg 100, NL-3584 CG Utrecht (NL). LISKAMP, Robertus, Mathais, Joseph [NL/NL]; Dept. of Medicinal Chemistry, Utrecht Institute for Pharmaceutical Sciences, Faculty of Pharmacy, Utrecht University, P.O. Box 80082, NL-3508 TB Utrecht (NL). KRUITZER, Johannes, Anna, Wilhelmus [NL/NL]; Dept. of Medicinal Chemistry, Utrecht

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WO 01/90140 A1

(54) Title: PEPTOIDS AS LIGANDS FOR MELANOCORTIN RECEPTORS

(57) Abstract: A peptoid having binding affinity for a melanocortin receptor, comprises the amino acid sequence AA₄-AA₅-AA₆-DAA₇-NAA₈-NAA₉-AA₁₀ wherein AA₄ and AA₅ are each absent or an amino acid; AA₆ is a basic amino acid; DAA₇ is a D-amino acid; NAA₈ and NAA₉ are each N-substituted amino acids; and AA₁₀ is absent or an amino acid.

PEPTOIDS AS LIGANDS FOR MELANOCORTIN RECEPTORS

Field of the Invention

This invention relates to peptoids that have binding activity for melanocortin receptors.

5 Background of the Invention

Melanocortins are peptides originally derived from a larger, precursor protein, i.e. pro-opiomelanocortin. Natural melanocortins share the heptapeptide core sequence Met-Glu-His-Phe-Arg-Trp-Gly. The melanocortins include α -MSH (α -melanocyte-stimulating hormone), β -MSH, γ -MSH, γ -LPH (γ -lipotropin hormone) and
10 ACTH (adrenocorticotrophic hormone).

Melanocortins have a wide range of biological activities. They are known to stimulate pigmentation and corticosteroidogenesis, and they have also been shown to induce excessive grooming behaviour in the rat, to stimulate conditioned active avoidance response, to increase blood pressure and heart rate, to accelerate nerve
15 regeneration and to modulate immune responses.

Five neuropeptide receptors for melanocortins have recently been identified and cloned. These receptors have different distribution patterns, both in presence and abundance, over different tissue types. They belong to the family of so-called G-protein-coupled receptors. Melanocortin receptor 1 (MCR-1) is expressed in
20 melanocytes, whereas MCR-2 is the ACTH receptor expressed in, for example, the adrenal gland. Melanocortin receptors 3, 4 and 5 have been found to be expressed in the central nervous system. The cognate ligands of these receptors have profound neuropharmacological effects, such as facilitated arousal, motivation, attention, memory and learning. The ligands have also been implicated in food-motivated behaviour. A
25 relationship with antipyretic activity has also been disclosed.

Many synthetic analogues of melanocortin have been prepared and suggested to have therapeutic utility, by activation or blocking of one or more melanocortin receptors. In general, such analogues lack specificity (selectivity) for the receptors expressed in the nervous system, and/or they lack sufficient binding affinity or capability
30 to induce or block the receptor-mediated response.

Peptides having melanocortin receptor-binding activity, and selectivity for MCR-3, MCR-4 or MCR-5, are described in WO-A-98/27113 and WO-A-99/54358. While active *in vitro*, these compounds are peptides that are unlikely to have sufficiently long half-life in plasma that they can be of therapeutic use.

Various strategies for rendering peptides resistant to breakdown *in vivo* are known. These include the use of D-amino acids and N-substituted amino acids, as in peptoids, but such strategies can severely compromise the specificity and efficacy of the compounds.

5 Summary of the Invention

According to the present invention, novel peptoids having binding affinity for a melanocortin receptor, and in particular the MC3, MC4 or MC5 receptor, comprise the amino acid sequence



wherein AA_4 and AA_5 are each absent or an amino acid;

AA_6 is a basic amino acid;

DAA_7 is a D-amino acid;

15 NAA_8 and NAA_9 are each N-substituted amino acids; and

AA_{10} is absent or an amino acid.

Surprisingly, it has been found that, provided that NAA_8 and NAA_9 , i.e. positions 8 and 9 (referring to the numbering of the amino acids in ACTH), both contain a peptoid building block, a satisfactory degree of potency is retained. In particular, potency is greater than if either position 8 or 9 alone, or position 7, includes a peptoid building block.

20 Description of the Invention

The term "amino acid" is used herein to describe, not only the 20 naturally occurring amino acids, but also derivatives and peptoid analogues thereof. The skilled man will appreciate that, in accordance with the intention behind this invention, i.e. to minimise loss of activity while increasing half-life, minimum values for each criterion should be retained, e.g. at least as good as for any exemplified compound of the invention. It may be expected that two juxtaposed naturally occurring amino acids will make the compound susceptible to hydrolysis; however, the loss of one or more amino acids from the compound may leave an active structure according to the invention.

30 In general, the structural characteristics of naturally occurring amino acids will be retained, in terms of the peptide backbone and side-chains, whether in a L-, D- or N-substituted form. Nevertheless, a variety of aromatic residues may be used, e.g. at position 7. F or Cl as a substituent can promote agonist activity; I as a substituent, or

a naphthalene or pentamethylenephényl residue, can provide enhanced antagonist activity.

The novel compounds are peptoids because the peptide side-chain at positions 8 and 9 at least is on the N atom, rather than the C atom, of the given amino acid in the peptide backbone. Such peptoid (non-chiral) building blocks may also be present at
5 any other position in the compound.

Certain compounds of the invention are preferred. It is preferred that AA₄ (if present) is NNle, Nle or Gly, that AA₅ (if present) is Gly or Asp, that AA₆ is NHis, NLys, His or Lys, that DAA₇ is D-Nal, D-Phe, D-PmP, D-Thi or D-Pyr, that NAA₈ is N-Arg, that
10 NNA₉ is N-Trp or a homologue thereof, that AA₁₀ (if present) is Gly or Lys, and/or that the compound is cyclised. In general, each preferred feature confers on the novel compound enhanced potency, half-life and/or selectivity.

Peptoids of this invention typically comprise at least three or four residues (corresponding to positions 6-9).

15 Peptoids of the invention can be made by standard procedures. The individual amino acids or analogues thereof are known or can be made by known procedures.

By way of explanation, this invention is based on comparison of the properties of a number of peptides/peptoids that have been synthesised; in particular, four peptoids illustrating the invention have been synthesised, using a robotic synthesiser,
20 and are given as SEQ ID NOS:1-4. These were then tested.

The tests, as well as synthetic procedures, are described in WO-A-98/27113. That publication also describes therapeutic indications that may be associated with the characteristics that are found in various tests, and appropriate compositions and dosage regimens. In general, compounds of this invention have longer half-lives, but
25 they may be less potent and therefore require higher dosages in order to obtain the same therapeutic effect.

CLAIMS

1. A peptoid having binding affinity for a melanocortin receptor, which comprises the amino acid sequence

5 AA₄-AA₅-AA₆-DAA₇-NAA₈-NAA₉-AA₁₀

wherein AA₄ and AA₅ are each absent or an amino acid;

AA₆ is a basic amino acid;

DAA₇ is a D-amino acid;

10 NAA₈ and NAA₉ are each N-substituted amino acids; and

AA₁₀ is absent or an amino acid.

2. A peptoid according to claim 1, wherein AA₄ (if present) is NNle, Nle or Gly.

3. A peptoid according to claim 1 or claim 2, wherein AA₅ (if present) is Gly or Asp.

4. A peptoid according to any preceding claim, wherein AA₆ is NHis, NLys, His or

15 Lys.

5. A peptoid according to any preceding claim, wherein DAA₇ is D-Nal, D-Phe, D-PmP, D-Thi or D-Pyr.

6. A peptoid according to any preceding claim, wherein NAA₈ is N-Arg.

7. A peptoid according to any preceding claim, wherein NAA₉ is N-Trp or a
20 homologue thereof.

8. A peptoid according to any preceding claim, wherein AA₁₀ (if present) is Gly or Lys.

9. A peptoid according to any preceding claim, which is cyclised.

10. A peptoid according to any preceding claim, for use in therapy.

SEQUENCE LISTING

<110> Quadrant Holdings Cambridge Limited

<120> PEPTOIDS

<130> REP06329WO

<140> NOT YET KNOWN

<141> 2001-05-22

<160> 4

<170> PatentIn Ver. 2.1

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<223> Description of Artificial Sequence: oligopeptide

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arginine, Pos. 6 is N-substituted homotryptophan

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N-substituted arginine, Pos. 6 - Xaa is
N-substituted homotryptophan

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<223> Description of Artificial Sequence: oligopeptide

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<222> (1)..(6)

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Pos. 5 is N-substituted arginine, Pos. 6 - Xaa is
N-substituted homotryptophan

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Xaa Gly Xaa Xaa Xaa Xaa Gly

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<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: oligopeptide

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<221> PEPTIDE

<222> (1)..(6)

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Xaa is N-substituted lysine, Pos. 4 - Xaa is
D-phenylalanine, Pos. 5 - Xaa is N-substituted
arginine, Pos. 6 - Xaa is N-substituted
homotryptophan

<400> 4

Xaa Gly Xaa Xaa Xaa Xaa Gly

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5

INTERNATIONAL SEARCH REPORT

In .onal Application No

PCT/GB 01/02282

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K7/02 A61K38/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE, CHEM ABS Data, EPO-Internal, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 131, no. 2, 12 July 1999 (1999-07-12) Columbus, Ohio, US; abstract no. 19270, HEIZMANN, G. ET AL: "A combinatorial peptoid library for the identification of novel MSH and GRP/bombesin receptor ligands" XP002177895	1,10
A	abstract & J. RECEPT. SIGNAL TRANSDUCTION RES. (1999), 19(1-4), 449-466 , --- -/--	2-9

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

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04/10/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

Döpfer, K-P

INTERNATIONAL SEARCH REPORT

Int.ional Application No

PCT/GB 01/02282

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 21571 A (TREGA BIOSCIENCES INC) 6 May 1999 (1999-05-06) page 3, line 1 - line 14 page 4, line 13 -page 17, line 12 claims; examples -----	1-10
A	WO 98 27113 A (ADAN ROGER ANTONIUS HENDRICUS ;GISPEN WILLEM HENDRIK (NL); BURBACH) 25 June 1998 (1998-06-25) cited in the application the whole document -----	1-10
A	WO 98 10068 A (UNIV OREGON HEALTH SCIENCES ;FAN WEI (US); LU DONGSI (US); BOSTON) 12 March 1998 (1998-03-12) claims -----	1-10
A	WO 99 54358 A (QUADRANT HOLDINGS CAMBRIDGE ;GISPEN WILLEM HENDRIK (NL); ADAN ROGE) 28 October 1999 (1999-10-28) the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 01/02282

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921571 A	06-05-1999	AU 7464998 A	17-05-1999
WO 9827113 A	25-06-1998	AU 5348098 A	15-07-1998
		CN 1246868 A	08-03-2000
		EP 0946595 A	06-10-1999
		JP 2001506996 T	29-05-2001
WO 9810068 A	12-03-1998	US 6100048 A	08-08-2000
		AU 719954 B	18-05-2000
		AU 4181297 A	26-03-1998
		EP 0935655 A	18-08-1999
		US 6278038 B	21-08-2001
WO 9954358 A	28-10-1999	AU 3615599 A	08-11-1999